

⑫

**EUROPEAN PATENT APPLICATION**

⑪ Application number: 86116398.2

⑫ Date of filing: 26.11.86

⑬ Int. Cl.<sup>4</sup>: **C 07 D 235/30**  
**C 07 D 235/28, C 07 D 235/1-**  
**8**  
**C 07 D 417/04, A 61 K 31/41-**  
**5**  
**A 61 K 31/425**

⑭ Priority: 27.11.85 US 802798

⑮ Date of publication of application:  
03.06.87 Bulletin 87/23

⑯ Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑰ Applicant: **SYNTEX (U.S.A.) INC.**  
**3401 Hillview Avenue P.O. Box 10850**  
**Palo Alto California 94303(US)**

⑱ Inventor: **Runkel, Richard Allen**  
**741 Garland Drive**  
**Palo Alto California 94303(US)**

⑲ Representative: **Barz, Peter, Dr. et al,**  
**Patentanwälte Dipl.-Ing. G. Dannenberg Dr. P. Weinhold,**  
**Dr. D. Gudel Dipl.-Ing. S. Schubert, Dr. P. Barz**  
**Siegfriedstrasse 8**  
**D-8000 München 40(DE)**

⑳ Amorphous benzimidazole derivatives.

㉑ Amorphous, non-crystalline forms of benzimidazole de-  
 rivatives have higher solubility and efficacy than crystalline  
 forms. Novel compositions are disclosed which prevent  
 crystallization of amorphous benzimidazole derivatives from  
 either solid or liquid form.

5

AMORPHOUS BENZIMIDAZOLE DERIVATIVES

10

This invention relates to amorphous benzimidazole derivatives which exhibit increased solubility and anthelmintic activity.

15 This invention also relates to a composition comprising an amorphous benzimidazole derivative and a stabilizing amount of a stabilizer polymer.

This invention also relates to a process for making the compounds and compositions of the invention, a method  
20 for stabilizing amorphous benzimidazole derivatives, a method for treating humans and other animals for helminthiasis and/or fascioliasis, and pharmaceutical and veterinary compositions therefor.

Related Disclosures

25 Benzimidazole derivatives with anthelmintic activity have long been known in the art. See, e.g., U.S. Pat. Nos. 3,017,415, 3,480,642, 3,574,845, 3,657,267, 3,915,986, 3,929,821, and 3,993,682. However, conventional benzimidazole derivatives are rarely soluble  
30 to a practical degree in pharmaceutically acceptable carriers. Most conventional benzimidazole derivatives are nearly insoluble in water. This presents problems both for formulation and for bioavailability.

35

It has long been assumed, since helminths infest the digestive tracts of the animals to be treated, that the benzimidazole derivative administered as anthelmintics need not enter the bloodstream to a significant extent.

5 Indeed, the bioavailability of benzimidazole derivatives is typically very low. The plasma uptake of benzimidazole derivatives administered to monogastric animals is usually 2% to 40% or less of the dose administered. The compound crystalline mebendazole is  
10 only 3-4% absorbed when administered to humans. Thus, doses as high as 1 g t.i.d. of crystalline mebendazole are required to treat conditions such as alveolar echinococcosis. It has now been found that the plasma concentration of a benzimidazole derivative is crucial to  
15 its efficacy, and that an increased plasma concentration correlates with increased anthelmintic activity. Other researchers have increased the initial plasma uptake of benzimidazole derivatives by wet-milling the powders to increase the surface area. (See for example EPO  
20 Application Ser. No. 147,767-A.) As a result, the plasma concentration of a benzimidazole may initially be high, but will decrease rapidly to the level obtained with unmilled crystalline powders.

25 It has now been found that one may increase the solubility and efficacy of benzimidazole derivatives by preparing them in an amorphous, non-crystalline form. The increased solubility results in relatively constant plasma concentration of benzimidazole derivative at a level much higher than that obtainable by increasing  
30 surface area, thus allowing one to decrease the dose and/or increase the effectiveness. This in turn allows one to treat strains of helminths resistant to the dose levels of anthelmintic benzimidazole derivatives presently administered. It has also been discovered that  
35 one may stabilize the amorphous form, (i.e., prevent

conversion of amorphous benzimidazole derivatives to crystalline benzimidazole derivatives) by forming a homogeneous composition of amorphous benzimidazole derivative and a stabilizer polymer. Said compositions  
5 may be either solid (e.g., powders or wet cakes) or liquid. Amorphous compositions of the invention are effective at doses 60% to 10% the effective dose of a crystalline benzimidazole derivative.

10

DEFINITIONS

The terms used in this Specification and the appended Claims have the following definitions unless specified otherwise.

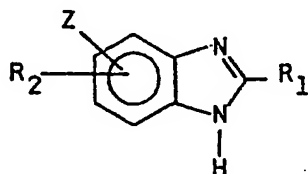
The term "amorphous" means substantially free of  
15 crystalline material wherein "substantially" means between 70% and 100% of the sample is amorphous, preferably between 80% and 100% of the sample is amorphous, more preferably between 90% and 100% of the sample is amorphous. Amorphous benzimidazole derivatives  
20 may be distinguished from crystalline forms by a number of methods, including differential scanning calorimetry, X-ray diffraction, microscopic examination, and dissolution comparison. For example, differential scanning calorimetry distinguishes amorphous mebendazole  
25 from crystalline mebendazole because amorphous mebendazole exhibits an exotherm at its melting point, whereas crystalline mebendazole exhibits an endotherm. X-ray diffractograms of crystalline mebendazole characteristically show several large peaks between 5°  
30 and 25° (plotting intensity vs. 2θ), whereas X-ray diffractograms of amorphous mebendazole exhibit small peaks, if any. Under microscopic examination with polarized light, crystalline mebendazole exhibits birefringence, whereas amorphous mebendazole does not.  
35 Using a Hanson dissolution apparatus with a pH 5.5

buffer, one can demonstrate that amorphous mebendazole is between 2 and 20 times more soluble than crystalline mebendazole. The amount of crystalline matter is measured by means known in the art, for example by X-ray diffraction. Thus, an X-ray diffractogram of an amorphous material will exhibit few if any peaks between 10° and 20° (2θ). The area of any peaks between 10° and 20° will be less than 10% of the area below the baseline of the X-ray diffractogram of an amorphous material under this definition.

The term "rapid precipitation" means the precipitation of a solid from solution at a rate sufficient to avoid crystallization. "Rapid addition" refer to the addition of a solution or reagent at a high rate of speed. Generally, addition is rapid if the solution or reagent is added within 10 minutes, preferably within 1 minute.

The term "anthelmintic" refers to compounds which are useful for treating helminthiasis in animals.

The term "benzimidazole derivative" refers to compounds of formula 1:



(1)

wherein

Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl of 3

to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms, phenyl, or naphthyl; and

$R_2$  is -H, R, or -XR, where X is O, S, -C(O)-, or -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or alkoxy.

The term "animal" refers to both human and non-human species.

The term "pharmaceutical composition" refers to compositions for the treatment of human or domestic animals, including without limitation cattle, swine, dogs and sheep.

The term "veterinary composition" refers to compositions for the treatment of non-human domestic animals, including without limitation cattle, horses, swine, dogs, sheep, and the like.

The term "pharmaceutically acceptable salt" refers to salts of the subject compounds which possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. These salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and the like. The term "pharmaceutically acceptable" includes all salts which are acceptable for human or veterinary use.

The term "effective amount" refers to the amount of benzimidazole derivative of formula 1 needed to effect treatment of a subject animal. The effective amount will vary from compound to compound. Generally, an effective amount of an amorphous compound of formula 1 will be

between 60% and 10% the effective amount of the compound in a crystalline form. An effective amount for compounds of formula 1 will generally be between about 0.02 mg/kg and 20 mg/kg. An effective amount of amorphous  
5 oxfendazole for cattle is generally between about 1 mg/kg and about 4 mg/kg, preferably between 2 mg/kg and 3 mg/kg, more preferably about 2.8 mg/kg. An effective amount of amorphous oxfendazole for sheep is generally  
10 between about 1 mg/kg and about 4 mg/kg, preferably between about 2 and 3.5 mg/kg, more preferably about 3 mg/kg. An effective amount of amorphous oxfendazole for swine is generally between about 2 mg/kg and about 8 mg/kg, preferably between 3 mg/kg and 5 mg/kg, more preferably about 4 mg/kg. An effective amount of  
15 amorphous oxfendazole for dogs is generally about 3 mg/kg. An amount of amorphous mebendazole effective for treating humans with alveolar echinococcosis is generally between about 100 and 300 mg/patient t.i.d.

The term "stabilizer polymer" refers to derivatives  
20 of compounds which are capable of preventing or inhibiting crystallization of benzimidazole derivatives. Stabilizer polymers include without limitation cellulosic derivatives, polyvinyl pyrrolidone and derivatives, xanthan gums, pectins, alginates, tragacanth and  
25 derivatives, Gum Arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, arabinogalactans, galactomannans, dextrans and the like. Preferred stabilizer polymers are cellulosic derivatives and xanthan gums. More preferred stabilizer  
30 polymers are cellulosic derivatives.

The term "cellulosic derivative" refers to  
derivatives of cellulose which are capable of preventing  
or inhibiting the crystallization of benzimidazole  
derivatives. Preferred cellulosic derivatives are  
35 non-toxic to the subject animal at the level at which

they are administered. Cellulosic derivatives include without limitation methyl cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, and the like. Preferred cellulosic derivatives are methyl cellulose, and sodium carboxymethylcellulose, especially methyl cellulose. Most preferred are Methocel® A4C Premium, Methocel® A-15 Premium (obtainable from Dow Chemical - USA), and sodium carboxymethylcellulose (CMC 7MF, obtainable from Hercules, Inc., Wilmington, Delaware).

The term "stable amorphous composition" refers to compositions containing an amorphous compound of formula 1 and a stabilizing amount of a stabilizer polymer. Thus, a stable amorphous composition is in a stable form, and resists the tendency to crystallize.

A "stabilizing amount" of a stabilizer polymer is the amount needed to prevent an amorphous compound of formula 1 from converting to a crystalline form. The stabilizing amount varies depending on the compound and the stabilizer polymer, but is between 0.0001 g/(g compound) and 0.9 g/(g compound), preferably between 0.001 g/(g compound) and 0.15 g/(g compound), more preferably between 0.02 g/(g compound) and 0.05 g/(g compound), and most preferably about 0.03 g/(g compound). It should be noted that the maximum amount of stabilizer polymer is governed only by economic or practical necessities. As a practical matter, a maximum amount of stabilizer polymer will be the maximum amount that may be administered without injury to the subject. Thus, typical ratios (percentages) of stabilizer polymer to compound of formula 1 needed to stabilize the compound of formula 1 include 0.001/1 (0.1%); 0.1/1 (10%); and 0.3/1 (30%).

The term "Keltrol®" refers to a xanthan gum which is commonly used in the pharmaceutical industry as a



thickener. Keltrol® is derived by fermentation of Xanthomonas compestris, and is available commercially from Kelco Co., San Diego, California. The preparation of Xanthan gums is described in U.S. Pat. Nos. 3,433,708  
5 and 3,557,016, incorporated herein by reference.

The term "Carbopol" refers to an acrylic acid polymer resin with an average equivalent weight of about 76. Carbopol is commonly used in the pharmaceutical industry as a suspending agent, and is available  
10 commercially.

The term "Masonex" refers to a hemicellulose extract by-product of Masonite board process. Masonex is a viscous, dark-colored syrup commonly used in the pharmaceutical industry as a drug carrier, and is  
15 commercially available.

The term "treatment" as used herein covers any treatment of a disease in a mammal, and includes:

(i) inhibiting the disease, i.e., arresting its development; or

20 (ii) relieving the disease, i.e., causing regression of the disease.

The term "crumble" refers to a granulated mixture comprising an active ingredient, corn syrup, and common feed, which is pelletized and crushed to produce  
25 particles less than about 5 mm in diameter.

The term "albendazole" refers to the compound methyl 5-(propylthio)-1H-benzimidazol-2-yl carbamate, also known as 5-n-propylthio-2-carbomethoxyaminobenzimidazole.

30 The term "fenbendazole" refers to the compound methyl 5-(phenylthio)-1H-benzimidazol-2-yl carbamate, also known as 5-phenylthio-2-carbomethoxyamino-benzimidazole.

The term "mebendazole" refers to the compound methyl 5-benzoyl-1H-benzimidazol-2-yl carbamate, also known as  
35 5-benzoyl-2-carbomethoxyaminobenzimidazole.

The term "oxibendazole" refers to the compound methyl 5-(1-propoxy)-1H-benzimidazol-2-yl carbamate, also known as 5-propoxy-2-carbomethoxyaminobenzimidazole.

5 The term "parbendazole" refers to the compound methyl 5-(1-butyl)-1H-benzimidazol-2-yl carbamate, also known as 5-(1-butyl)-2-carbomethoxyaminobenzimidazole.

The term "flubendazole" refers to the compound methyl 5-(4-fluorobenzoyl)-1H-benzimidazol-2-yl carbamate, also known as  
10 5-(4-fluorobenzoyl)-2-carbomethoxyamino- benzimidazole.

The term "cyclobendazole" refers to the compound methyl 5-cyclopropylcarbonyl-1H-benzimidazol-2-yl carbamate, also known as 5-cyclopropylcarbonyl-2-carbomethoxyaminobenzimidazole.

15 The term "thiabendazole" refers to the compound methyl 2-(4-thiazolyl)-1H-benzimidazole.

The term "cambendazole" refers to the compound isopropyl 2-(4-thiazolyl)-1H-benzimidazol-5-yl carbamate.

The term "triclabendazole" refers to the compound  
20 6-chloro-5-(2,5-dichlorophenoxy)-2-methylthiobenzimidazole.

The term "oxfendazole" refers to the compound methyl 5-(phenylsulfinyl)-1H-benzimidazol-2-yl carbamate, also known as 5-phenylsulfinyl-2-carbomethoxyamino-  
25 benzimidazole.

The term "alkyl" refers to a saturated hydrocarbon radical containing 1 to 20 carbon atoms. "Lower alkyl" refers to an alkyl radical of 1 to 6 carbons, for example, methyl, ethyl, n-propyl, i-propyl, butyl, s-butyl, pentyl, hexyl.  
30

The term "cycloalkyl" refers to a cyclic saturated hydrocarbon radical containing 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

35

-10-

The term "alkenyl" refers to a hydrocarbon radical of 3 to 7 carbon atoms, containing a double bond, for example, propenyl, allyl, butenyl, pentenyl, hexenyl, heptenyl.

5 The term "alkynyl" refer to a hydrocarbon radical of 3 to 7 carbon atoms, containing a triple bonds, for example, propynyl, propargyl, butynyl, pentynyl, hexynyl, heptynyl.

10 The term "alkoxy" refers to a radical of the form RO-, where R is lower alkyl or cycloalkyl as defined above.

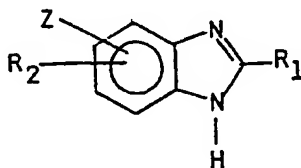
The term "aryl" refers to an aromatic hydrocarbon radical containing 6 carbon atoms, a phenyl ring.

15 The term "aryl-alkyl" refers to an aryl group to which a lower alkyl group as defined above is attached.

The term "halo" refers to fluoro, chloro, bromo, or iodo.

20 One aspect of the invention is a benzimidazole derivative of formula 1 or a pharmaceutically acceptable salt thereof in an amorphous (non-crystalline) form:

25



(1)

30 wherein Z is -H or halo; R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl;  
35 and R<sub>2</sub> is -H, R, or -XR, where X is O, S, -C(O)-, or

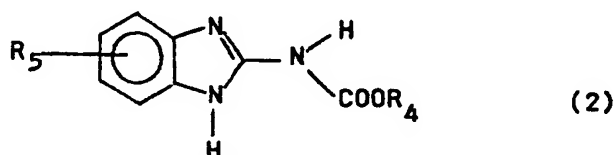
1804Y

25320-FF

-NHC(=O)O-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or alkoxy.

Another aspect of the invention is a combination of  
 5 benzimidazole derivatives, comprising an amorphous compound of formula 1 and a different amorphous compound of formula 1 or an amorphous compound of formula 2;

10



or a pharmaceutically acceptable salt thereof,  
 15 wherein  $R_4$  is lower alkyl; and  $R_5$  is  $-S(O)_m R_6$ ,  $-OR_6$ , or  $-Y_1(CH_2)_n Y_2 R_7$  where  $Y_1$  and  $Y_2$  are each independently O, S, or  $S(O)$ ,  $R_7$  is lower alkyl, phenyl, or naphthyl, and  $n$  is 1, 2, 3, or 4;  $R_6$  is lower alkyl, cycloalkyl, alkenyl of 3 to 7 carbon  
 20 atoms, alkynyl of 3 to 7 carbon atoms, phenyl, benzyl, phenylethyl, or naphthyl; and  $m$  is 0 or 1.

Another aspect of the invention is a stable  
 amorphous composition comprising a stabilizing amount of  
 a stabilizer polymer and an amorphous compound of  
 25 formula 1.

Another aspect of the invention is a stable  
 amorphous composition comprising a stabilizing amount of  
 a stabilizer polymer, an amorphous compound of formula 1,  
 and a different amorphous compound of formula 1 or  
 30 formula 2.

Another aspect of the invention is a process for  
 producing amorphous benzimidazole derivatives, which  
 process comprises precipitating a benzimidazole  
 derivative of formula 1 from an acidic or basic solution  
 35 by rapidly adding an amount of base or acid sufficient to

adjust the solution to the pH of lowest benzimidazole solubility.

Another aspect of the invention is a process for producing stable amorphous compositions, which process  
5 comprises rapidly precipitating a benzimidazole derivative of formula 1, or a combination of benzimidazole derivatives of formula 1 and/or formula 2 from an acidic or basic solution by adding a basic or acidic solution containing a stabilizing amount of a  
10 stabilizer polymer.

Another aspect of the invention is a process for producing stable amorphous compositions, which process comprises spray drying a benzimidazole derivative of formula 1, or a combination of benzimidazole derivatives  
15 of formula 1 and/or formula 2 from an acidic or basic solution containing a stabilizing amount of a stabilizer polymer.

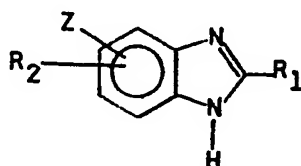
Another aspect of the invention is a pharmaceutical or veterinary composition for the treatment of  
20 helminthiasis and/or fascioliasis, which composition comprises a stabilizing amount of a stabilizer polymer; and an amorphous compound of formula 1, a combination of amorphous compounds of formula 1, or a combination of an amorphous compound of formula 1 and an amorphous compound  
25 of formula 2.

Another aspect of the invention is a method of treating an animal for helminthiasis and/or fascioliasis, which method comprises administering to a mammal in need thereof an effective amount of an amorphous anthelmintic composition of formula 1, or a combination of amorphous  
30 anthelmintic compositions of formula 1 and/or formula 2.

Another aspect of the invention is the use of an amorphous compound of formula 1, a combination of amorphous compounds of formula 1, or a combination of an amorphous compound of formula 1 and an amorphous compound  
35

of formula 2 to prepare a pharmaceutical or veterinary composition for the treatment of helminthiasis and/or fascioliasis.

Another aspect is a process for preparing an  
5 amorphous anthelmintic compound of formula 1



(1)

or a pharmaceutically acceptable salt, wherein Z is  
-H or halo;  $R_1$  is a five-membered heteroaromatic  
15 ring containing 1, 2, or 3 heteroatoms selected from  
O, N, and S; or  $R_1$  is  $-SCH_3$ ,  $-NHCOOR_3$ ,  
 $-NHCSOR_3$ , or  $-NHCOSR_3$  where  $R_3$  is alkyl,  
cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl;  
and  $R_2$  is H, R, or  $-XR$ , where X is O, S,  $-C(O)-$ ,  
20 or  $-NHCOO-$ ; and R is alkyl, cycloalkyl, aryl or  
aryl-alkyl, optionally substituted with halo, alkyl,  
hydroxy, or alkoxy,

which process comprises:

A. (a) dissolving a compound of formula 1 in a  
25 base or acid to dissolve or solubilize said compound of  
formula 1, followed by

(b) adding an amount of an acid or base under  
conditions to precipitate said compound of formula 1 in  
an amorphous form; or

30 B. (a) dissolving a compound of formula 1 in an  
acid or base to dissolve or solubilize said compound of  
formula 1, followed by

(b) spray drying the solution of step (a) to  
produce an amorphous compound of formula 1; or

35

C. (a) dissolving a compound of formula 1 in an acid or base solution containing a stabilizing amount of a stabilizer polymer, followed by

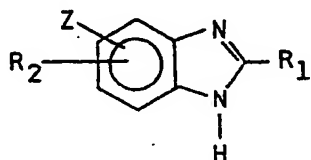
(b) spray drying the solution of step (a) to produce an amorphous compound of formula 1; or

D. (a) dissolving a compound of formula 1 in an acid or base within a first pH range to dissolve or solubilize said compound of formula 1, followed by

(b) adding a stabilizing amount of a stabilizer polymer in a solution of a second pH range opposite to that used in step (a), followed by

(c) adding acid or base to reestablish a third acid or base pH range on the same side of the pH scale as said first pH range to form an amorphous form of a compound of formula 1.

One aspect of the invention is a benzimidazole derivative of formula 1 or a pharmaceutically acceptable salt thereof in an amorphous (non-crystalline) form:



(1)

wherein

Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

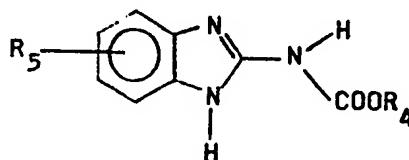
$R_2$  is -H, R, or -XR, where X is O, S, -C(O)-, or -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or alkoxy.

- 5 A preferred subgenus of the invention is the amorphous compound of formula 1 wherein  $R_1$  is -NHCOOR<sub>3</sub>, particularly where  $R_3$  is methyl. A preferred class of the invention is that wherein  $R_2$  is of the form -XR, especially where X is S. Preferred species are those wherein R is n-propyl or phenyl.
- 10 Another preferred subclass of the invention is that wherein X is -C(O). Preferred species are those wherein R is cyclopropyl, phenyl or 4-fluorophenyl. Another preferred subclass of the invention is that wherein X is O.
- 15 A preferred species is that wherein R is n-propyl. Another preferred class of the invention is that wherein  $R_2$  is alkyl. A preferred species is that wherein R is 1-butyl.

- Another preferred subgenus of the invention is the amorphous compound of formula 1 wherein  $R_1$  is 4-thiazolyl. A preferred species is that wherein  $R_2$  is H. A preferred class is that wherein  $R_2$  is -XR, especially where X is -NHCOO. A preferred species is that wherein  $R_2$  is 2-propyl.

- 25 Another aspect of the invention is a combination of amorphous benzimidazole derivatives, comprising a combination of amorphous compounds of formula 1 or a combination of an amorphous compound of formula 1 and an amorphous compound of formula 2;

30



(2)

35

1804Y

25320-FF



-16-

or a pharmaceutically acceptable salt thereof,  
wherein

- $R_4$  is lower alkyl; and  
 $R_5$  is  $-S(O)_m R_6$ ,  $-OR_6$ , or  
 5  $-Y_1(CH_2)_n Y_2 R_7$  where  
 $Y_1$  and  $Y_2$  are each independently O, S, or  
 $S(O)$ ,  $R_7$  is lower alkyl, phenyl, or naphthyl, and  
 $n$  is 1, 2, 3, or 4;  
 $R_6$  is lower alkyl, cycloalkyl, alkenyl of 3  
 10 to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms,  
 phenyl, benzyl, phenylethyl, or naphthyl; and  
 $m$  is 0 or 1.

A preferred subgenus of the invention is the  
 15 combination comprising an amorphous compound of formula 1  
 and an amorphous compound of formula 2, especially where  
 $R_4$  is methyl. A preferred class of the invention is  
 that wherein  $R_5$  is  $-S(O)R_6$ , particularly where  $R_6$   
 is phenyl or n-propyl, especially wherein the compound of  
 20 formula 2 is oxfendazole. A preferred species is the  
 combination wherein the amorphous compound of formula 1  
 is triclabendazole.

Another aspect of the invention is a stable  
 amorphous composition comprising a stabilizing amount of  
 25 a stabilizer polymer and an amorphous compound of  
 formula 1. A preferred subgenus of the invention is the  
 amorphous compound of formula 1 wherein  $R_1$  is  
 $-NHCOOR_3$ , particularly where  $R_3$  is methyl. A  
 preferred class of the invention is that wherein  $R_2$  is  
 30 of the form  $-XR$ , especially where  $X$  is S. Preferred  
 species are those wherein  $R$  is n-propyl or phenyl.  
 Another preferred subclass of the invention is that  
 wherein  $X$  is  $-C(O)$ . Preferred species are those wherein  
 $R$  is phenyl or 4-fluorophenyl. Another preferred  
 35 subclass of the invention is that wherein  $X$  is O. A

preferred species is that wherein R is n-propyl. Another preferred species is that wherein R is  $-\text{SCH}_3$  and Z is  $-\text{Cl}$ . Another preferred class of the invention is that wherein  $\text{R}_2$  is alkyl. A preferred species is that  
5 wherein R is 1-butyl.

Another preferred subgenus of the invention is the amorphous compound of formula 1 wherein  $\text{R}_1$  is  $-\text{SCH}_3$ . A preferred class of the invention is that wherein  $\text{R}_2$  is of the form  $-\text{XR}$ , especially where X is O. A preferred  
10 subclass of the invention is that wherein R is 2,3-dichlorophenyl. A preferred species is that wherein Z is  $-\text{Cl}$ .

Another preferred subgenus of the invention is the amorphous compound of formula 1 wherein  $\text{R}_1$  is  
15 4-thiazolyl. A preferred species is that wherein  $\text{R}_2$  is H. A preferred class is that wherein  $\text{R}_2$  is  $-\text{XR}$ , especially where X is  $-\text{NHCOO}$ . A preferred species is that wherein  $\text{R}_2$  is 2-propyl.

Another aspect of the invention is a stable  
20 amorphous composition comprising  
a stabilizing amount of a stabilizer polymer; and  
a combination of amorphous compounds of formula 1,  
or a combination of an amorphous compound of  
formula 1 and an amorphous compound of formula 2.  
25 A preferred subgenus of the invention is that comprising  
a stabilizing amount of a stabilizer polymer, an  
amorphous compound of formula 1 and an amorphous compound  
of formula 2, especially where  $\text{R}_4$  is methyl. A  
preferred class of the invention is that wherein  $\text{R}_5$  is  
30  $-\text{S}(\text{O})\text{R}_6$ , particularly where  $\text{R}_6$  is phenyl or  
n-propyl. A preferred species of the invention is the  
composition wherein said compound of formula 1 is  
triclabendazole and said compound of formula 2 is  
oxfendazole.

35

Another aspect of the invention is a process for producing amorphous benzimidazole derivatives, which process comprises rapidly precipitating a compound of formula 1 from an acidic or basic solution having a first pH by adjusting the pH of said solution to a second pH at which the compound of formula 1 has lower solubility. A preferred class is the process wherein said second pH is about the pH of minimum solubility of the crystalline benzimidazole derivative selected (usually about 4 to 6), especially where said first pH is between 8 and 11. A preferred subclass is the process wherein said compound of formula 1 is first formed or dissolved in a solution with a pH lower than 4 (especially where said solution is acetic acid, propionic acid, hydrochloric acid, phosphoric acid, formic acid or nitric acid; preferably concentrated formic acid or hydrochloric acid, particularly concentrated formic acid), followed by addition of base to raise the pH to about 8 (especially where said base is an organic or inorganic base such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium methylate, sodium ethylate, sodium hydride, triethylamine or pyridine; preferably ammonium hydroxide or sodium hydroxide in aqueous or methanolic solution; more preferably ammonium hydroxide or sodium hydroxide in aqueous solution), followed by addition of a second acid to lower the pH to about 5 (preferably where said second acid is the same acid as the first acid, especially where said second acid is concentrated formic acid). Another preferred subclass is the method in which said compound of formula 1 is first formed or dissolved in a solution with a pH higher than 7.5 (preferably where said solution is aqueous or methanolic organic or inorganic base such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium

methyllate, sodium ethyllate, sodium hydride, triethylamine or pyridine; preferably ammonium hydroxide or sodium hydroxide in aqueous or methanolic solution; more preferably ammonium hydroxide or sodium hydroxide in aqueous solution), followed by addition of a concentrated acid to lower the pH to about 5 (especially where said acid is acetic acid, propionic acid, hydrochloric acid, phosphoric acid, formic acid or nitric acid; preferably concentrated formic acid or hydrochloric acid; more preferably concentrated formic acid).

Another aspect of the invention is a process for producing amorphous benzimidazole derivatives, which process comprises spray drying a compound of formula 1 from a solution, especially an acidic solution. A preferred class is the process wherein said acidic solution comprises concentrated formic acid and a compound of formula 1.

Another aspect of the invention is a process for producing stable amorphous benzimidazole compositions, which process comprises rapidly precipitating a compound of formula 1 and a stabilizing amount of a stabilizer polymer from an acidic or basic solution having a first pH by adjusting the pH of said solution to a second pH at which the compound of formula 1 has lower solubility. A preferred class is the process wherein said second pH is about 5, especially where said first pH is between 8 and 11. A preferred subclass is the process wherein said compound of formula 1 is first formed or dissolved in a solution with a pH lower than 4 (especially where said solution is concentrated formic acid or hydrochloric acid, particularly concentrated formic acid), followed by addition of base and a stabilizing amount of a stabilizer polymer to raise the pH to about 8 (especially where said base is aqueous or methanolic ammonium hydroxide or sodium hydroxide, particularly aqueous sodium hydroxide),

followed by addition of a second acid to lower the pH to about 5 (especially where said second acid is concentrated formic acid). Another preferred subclass is the method in which said compound of formula 1 is first  
5 formed or dissolved in a solution with a pH higher than 7.5 containing a stabilizing amount of a stabilizer polymer (especially where said solution is aqueous or methanolic ammonium hydroxide or sodium hydroxide, particularly aqueous sodium hydroxide), followed by  
10 addition of an acid to lower the pH to about 5 (especially where said acid is concentrated formic acid).

Another aspect of the invention is a process for producing stable amorphous benzimidazole compositions, which process comprises spray drying a compound of  
15 formula 1 and a stabilizing amount of a stabilizer polymer from a solution, especially an acidic or basic solution, particularly an acidic solution. A preferred class is the process wherein said solution comprises concentrated formic acid, a stabilizing amount of a  
20 stabilizer polymer, and a compound of formula 1.

Another aspect of the invention is a process for stabilizing benzimidazole derivatives or combinations of benzimidazole derivatives in an amorphous form, which  
25 process comprises rapidly precipitating a compound of formula 1, a combination of compounds of formula 1, or a combination of compounds of formula 1 and formula 2 from an acidic or basic solution by addition of a basic or acidic solution containing a stabilizing amount of a  
stabilizer polymer.

Another aspect of the invention is a method of  
30 treating an animal for helminthiasis and/or fascioliasis, which method comprises administering to a mammal in need thereof an effective amount of a composition comprising:  
a stabilizing amount of a stabilizer polymer; and

35

an amorphous compound of formula 1, a combination of amorphous compounds of formula 1, or a combination of an amorphous compound of formula 1 and an amorphous compound of formula 2.

5 Another aspect of the invention is a pharmaceutical or veterinary composition for the treatment of helminthiasis and/or fascioliasis, which composition comprises:

10 a stabilizing amount of a stabilizer polymer; and an amorphous compound of formula 1, or a combination of amorphous compounds of formula 1, or a combination of an amorphous compound of formula 1 and an amorphous compound of formula 2.

15 Another aspect of the invention is the use of an amorphous compound of formula 1 or an amorphous compound of formula 2 to prepare a pharmaceutical or veterinary composition for the treatment of helminthiasis and/or fascioliasis.

20

#### ADMINISTRATION

These compositions are effective when administered to the digestive system of a subject, for example orally or intraruminally. When the subject is a ruminant, it is preferred to administer the compositions of the invention 25 intraruminally.

In view of the foregoing as well as in consideration of the degree of severity of the condition being treated, age of subject and so forth, the effective dosage in accordance herewith can vary over a wide range.

30 Generally, a therapeutically effective amount ranges from about 0.02 to about 20 mg/kg body weight for amorphous compounds of the invention. Generally, a therapeutically effective amount ranges from about 1 to about 12 mg/kg body weight for amorphous fenbendazole. Other amorphous 35 benzimidazole derivatives may have varying dosage

ranges. Preferably, amorphous fenbendazole is administered intraruminally to cattle in dosages of about 5 mg/kg body weight. In other terms, for a 100 kg subject, a therapeutically effective amount in accordance herewith would be, in preferred embodiments from about 100 mg to about 1200 mg of amorphous fenbendazole per subject, and preferably about 500 mg per subject.

Preferably, amorphous fenbendazole is administered orally to sheep in dosages between 1 mg/kg and 6 mg/kg, preferably about 4.5 mg/kg body weight. In other terms, for a 30 kg subject, a therapeutically effective amount in accordance herewith would be, in preferred embodiments from about 30 mg to about 180 mg of amorphous fenbendazole per subject, and preferably about 135 mg per subject.

Preferably, amorphous mebendazole is administered orally to humans in dosages of between 20 mg/kg and 180 mg/kg TID, preferably about 40 mg/kg body weight.

#### PREPARATION OF THE INVENTION

Albendazole, fenbendazole, mebendazole, oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, cambendazole, triclabendazole, oxfendazole and certain other benzimidazole derivatives are available from commercial sources. Alternatively, one may prepare such compounds and their variations by the methods disclosed in the patent literature.

Albendazole, parbendazole, oxibendazole and similar benzimidazole derivatives may be made by the process described in U.S. Pat. No. 3,574,845, which is incorporated herein by reference. Fenbendazole and similar benzimidazole derivatives may be made by methods known in the art; see, e.g., Belgian Pat. No. 793,358. Thiabendazole and similar benzimidazole derivatives may be made by the process described in U.S. Pat. No. 3,017,415, which is incorporated herein by reference.

Flubendazole, mebendazole, cyclobendazole, and similar benzimidazole derivatives may be made by the process described in U.S. Pat. No. 3,657,267, which is incorporated herein by reference. Triclabendazole and  
5 similar benzimidazole derivatives may be made by the process described in U.S. Pat. No. 4,197,307, which is incorporated herein by reference. Cambendazole and similar benzimidazole derivatives may be made by methods known in the art; see, e.g., South African Pat. No.  
10 6,800,351. Oxfendazole and similar benzimidazole derivatives may be made by the process described in U.S. Pat. No. 3,929,821, which is incorporated herein by reference.

Stabilizer polymers are commercially available. For  
15 example, methylcellulose may be purchased from Dow Chemical under the trademark Methocel® A-15 or Methocel® A4C. Hydroxypropylcellulose may be purchased from Dow Chemical under the trademark Methocel® E-15 or Methocel® E-5. Sodium carboxymethylcellulose may be  
20 obtained from Hercules, Inc., under the designation CMC 7MF.

Amorphous compounds of formula 1 can be prepared by a variety of methods, characterized by the fact that the compound of formula 1 is precipitated rapidly and is not  
25 allowed time to equilibrate and crystallize. For example, a compound of formula 1 may be precipitated from solution by adding a solvent in which said compound does not dissolve or, preferably, by any of the following methods:

30 In the first method, a compound of formula 1 is dissolved or prepared in an acidic solution having a pH lower than about 3. Presently preferred solvents are concentrated hydrochloric acid, phosphoric acid, propionic acid, acetic acid, and formic acid; preferably  
35 hydrochloric acid and concentrated formic acid; more



preferably concentrated formic acid. The amorphous compound of formula 1 can be precipitated directly from the resulting acidic solution by the rapid addition of base with stirring. However, due to the solubility characteristics of the compounds involved, it is preferred to first basify the solution to a pH of about 8, taking care not to induce precipitation. The acidic solution may be basified with any strong base, for example ammonium hydroxide or sodium hydroxide in water or alcohol (such as methanol), preferably ammonium hydroxide or sodium hydroxide in water. The resulting basic solution is then acidified until the pH of the solution is about the pH of minimum benzimidazole solubility, a pH of about 4 to 5. The basic solution may be acidified with any concentrated acid, preferably concentrated formic acid. The resulting solution is then stirred until amorphous compound of formula 1 aggregates and precipitates, whereupon it is collected, washed and dried. For example, crystalline fenbendazole (10 g) is dissolved in concentrated formic acid (95-97%, 50 mL). A solution of NaOH (86 g) in water (5 L) is then slowly added (e.g., at about 60 mL/minute) with high shear mixing, taking care to avoid incorporating air or precipitation. Concentrated formic acid (about 50 mL) is then added with stirring until the pH of the resulting solution reaches 4 to 5. The solution is stirred until at least 90% of the amorphous fenbendazole precipitates. The precipitate is collected by vacuum filtration, washed with distilled water, and dried to yield amorphous fenbendazole.

In the second method, a compound of formula 1 is first dissolved in a basic aqueous or alcoholic solution. The base may be any strong base, such as ammonium hydroxide, sodium hydroxide, potassium hydroxide and the like. The resulting basic solution is then

acidified until the pH of the solution is about the pH of minimum benzimidazole solubility, a pH of about 4 to 5. The basic solution may be acidified with any concentrated acid, preferably concentrated formic acid. The resulting

5 solution is then stirred until amorphous compound of formula 1 aggregates and precipitates, whereupon it is collected, washed and dried. For example, crystalline fenbendazole (10 g) is dissolved in a solution of NaOH (86 g) in water (5 L). Concentrated formic acid is then  
10 added with stirring until the pH of the resulting solution reaches 4 to 5. The solution is stirred until amorphous fenbendazole precipitates. The precipitate is collected by vacuum filtration, washed with distilled water, and dried to yield amorphous fenbendazole.

15 In the third method, a compound of formula 1 is dissolved or prepared in an acidic solution having a pH lower than about 3. Any of the above listed acids can be used; preferred solvents are concentrated hydrochloric acid and formic acid; concentrated formic acid is most  
20 preferred. The amorphous compound of formula 1 is then spray dried to produce an amorphous compound of formula 1. For example, crystalline fenbendazole (10 g) is dissolved in concentrated formic acid (95-97%, 50 mL) and spray dried to yield amorphous fenbendazole.

25 Stable amorphous compositions of the invention can be prepared by any of the following methods:

In the first method, a compound of formula 1 is dissolved or prepared in an acidic solution having a pH lower than about 3. Presently preferred solvents are  
30 concentrated hydrochloric acid, phosphoric acid, propionic acid, acetic acid, nitric acid, and formic acid; concentrated formic acid is most preferred. The amorphous compound of formula 1 can be precipitated directly from the resulting acidic solution by the rapid  
35 addition of base with stirring, however, due to the

solubility characteristics of the compounds involved, it is preferred to first basify the solution to a pH of about 8 using a solution containing a stabilizing amount of a stabilizer polymer, taking care not to induce precipitation. The acidic solution may be basified with any strong base, for example ammonium hydroxide or sodium hydroxide in water or alcohol (such as methanol), preferably ammonium hydroxide or sodium hydroxide in water. The stabilizer polymer is preferably a cellulosic derivate, more preferably methylcellulose or sodium carboxymethylcellulose, particularly methylcellulose. The resulting basic solution is then acidified until the pH of the solution is about the pH of minimum benzimidazole solubility, a pH of about 4 to 5. The basic solution may be acidified with any concentrated acid, preferably concentrated formic acid. The resulting solution is then stirred until the amorphous composition precipitates and aggregates, whereupon it is collected, washed and dried. For example, crystalline fenbendazole (10 g) is dissolved in concentrated formic acid (95-97%, 50 mL). A solution of NaOH (86 g) and methylcellulose (10.0 g) in water (5 L) is then slowly added (e.g., at about 60 mL/minute) with high shear mixing, taking care to avoid incorporating air or inducing precipitation. Concentrated formic acid (about 50 mL) is then added with stirring until the pH of the resulting solution reaches 4 to 5. The solution is stirred until stabilized amorphous fenbendazole precipitates. The precipitate is collected by vacuum filtration, washed with distilled water, and dried to yield the stable amorphous composition of the invention.

In the second method, a compound of formula 1 is first dissolved in a basic aqueous or alcoholic solution containing a stabilizing amount of a stabilizer polymer. The base may be any strong base, such as ammonium

hydroxide, sodium hydroxide, potassium hydroxide and the like. The stabilizer polymer is preferably a cellulosic derivative, more preferably methylcellulose or sodium carboxymethylcellulose, particularly methylcellulose.

- 5 The resulting basic solution is then acidified until the pH of the solution is about the pH of minimum benzimidazole solubility, a pH of about 4 to 5. The basic solution may be acidified with any concentrated acid, preferably concentrated formic acid. The resulting
- 10 solution is then stirred until the stabilized amorphous composition of the invention aggregates and precipitates, whereupon it is collected, washed and dried. For example, crystalline fenbendazole (10 g) and Methocel® A4C (10.0 g) is dissolved in a solution of NaOH (86 g) in
- 15 water (5 L). Concentrated formic acid is then added with stirring until the pH of the resulting solution reaches 4 to 5. The solution is stirred until the amorphous composition precipitates. The precipitate is collected by vacuum filtration, washed with distilled water, and
- 20 dried to yield stabilized amorphous fenbendazole.

- In the third method, a stabilizing amount of a stabilizer polymer and a compound of formula 1 are dissolved or prepared in an acidic solution having a pH lower than about 3. Presently preferred solvents are
- 25 concentrated HCl and formic acid; concentrated formic acid is most preferred. The solution is then spray dried to produce a stabilized amorphous composition of the invention. For example, crystalline fenbendazole (10 g) and Methocel® A-15 (10.0 g) are dissolved in
- 30 concentrated formic acid (95-97%, 50 mL) and spray dried to yield stabilized amorphous fenbendazole.

- The methods described above may also be performed using mixtures of compounds of formula 1, or with mixtures of compounds of formula 1 and compounds of
- 35 formula 2 instead of using a single compound of

formula 1. These methods can be performed at ambient temperature and pressure.

The following specific description is given to enable those skilled in the art to more clearly understand and practice the invention. It should not be considered as a limitation upon the scope of the invention, but merely as being illustrative and representative thereof.

#### EXAMPLE 1

(Preparation of Amorphous Compounds And Compositions)

(A) Ten grams of crystalline fenbendazole is dissolved in 50 mL of formic acid (95-97%). A solution of 86 g NaOH in 5 L distilled water is then slowly added to the fenbendazole solution over about 90 minutes with high shear mixing, taking care to avoid air incorporation or precipitation. Concentrated formic acid is then added with stirring until the pH is between 4 and 5. The resulting solution is stirred until the amorphous fenbendazole aggregates, whereupon it is collected by vacuum filtration, washed with distilled water, and dried.

Samples of amorphous fenbendazole are prepared following the procedure above, and are finely ground. The diffractograms are obtained using a Nicolet Model 12 X-ray Diffractometer using CuK $\alpha$  radiation, scanning from 3° to 30° 2 $\theta$ , step width = 0.05°, step time = 2 seconds. A sample planchet of 0.016 is used. The sample is placed on the planchet and smoothed with a glass slide. The number of counts above background is obtained via computer analysis. The total peak area between 10° and 20° 2 $\theta$  using amorphous fenbendazole is compared with the total peak area between 10° and 20° 2 $\theta$  obtained using crystalline fenbendazole. The peak area from amorphous fenbendazole is less than 10% of the peak area obtained from crystalline fenbendazole.

(B) Similarly, proceeding as in part A above but substituting albendazole, mebendazole, oxbendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, tricloabendazole or cambendazole for fenbendazole, the corresponding amorphous compounds are produced. The peak area from amorphous each of these amorphous compounds is less than 10% of the peak area obtained from corresponding crystalline compound.

10

EXAMPLE 2

(A) Crystalline fenbendazole (10 g) is dissolved in formic acid (95-97%, 50 mL). A solution of NaOH (86 g) and methylcellulose (10.0 g, Methocel® A-15 Premium, Dow Chemical - USA) in distilled water (5 L) is then slowly added to the fenbendazole solution with high shear mixing, taking care to avoid air incorporation and precipitation. Concentrated formic acid is then added with stirring until the pH is between 4 and 5. The resulting solution is stirred until the amorphous fenbendazole-methylcellulose composition aggregates, whereupon it is collected by vacuum filtration, washed with distilled water, and dried.

Samples of amorphous fenbendazole-methylcellulose are prepared following the procedure above, and are finely ground. The diffractograms are obtained using a Nicolet Model 12 X-ray Diffractometer using CuK $\alpha$  radiation, scanning from 3° to 30° 2 $\theta$ , step width = 0.05°, step time = 2 seconds. A sample planchet of 0.016 is used. The sample is placed on the planchet and smoothed with a glass slide. The number of counts above background is obtained via computer analysis. The total peak area between 10° and 20° 2 $\theta$  using amorphous fenbendazole is compared with the total peak area between 10° and 20° 2 $\theta$  obtained using crystalline fenbendazole. The peak

1804Y

25320-FF

area from amorphous fenbendazole is less than 10% of the peak area obtained from crystalline fenbendazole.

(B) One gram of crystalline albendazole is dissolved in 3 ml of formic acid (95-97%). A 2% methylcellulose solution in 5°C distilled water containing 4 grams of sodium hydroxide is added slowly with good mixing. Eleven ml of formic acid (95-97%) at 5°C is added to adjust the pH to about 3. The pH is reduced to 1 by the addition of 16.5 ml of hydrochloric acid. A solution of 40% sodium hydroxide (47 ml at 5°C) is added to adjust the pH to 4.5, causing precipitation of the amorphous albendazole. The precipitate is centrifuged at 5°C, and dried. An X-ray diffractogram of the resulting sample showed the peak area from amorphous albendazole to be less than 10% of the peak area obtained from crystalline albendazole.

(C) One gram of crystalline triclabendazole is dissolved in 3 ml of formic acid (95-97%). With good stirring, this solution is slowly added to 1 liter of distilled water containing 4 grams of sodium hydroxide and 5 grams of methylcellulose. The pH of the resulting solution is adjusted to 4.5 with slow addition of concentrated formic acid. The mixture is stirred until the precipitate aggregates, whereupon it is collected by vacuum filtration and vacuum dried at ambient temperature. An X-ray diffractogram of the resulting sample showed the peak area from amorphous triclabendazole to be less than 10% of the peak area obtained from crystalline triclabendazole.

(D) Two grams of crystalline mebendazole is dissolved in 20 ml of formic acid (95-97%). With good stirring, the formic acid solution is slowly added to 1 liter of distilled water containing 32 grams of sodium hydroxide and 4 grams of methylcellulose. The pH of the resulting solution is slowly adjusted to 4.5 using

concentrated formic acid. The resulting precipitate is centrifuged and dried. An X-ray diffractogram of the resulting sample showed the peak area from amorphous mebendazole to be less than 10% of the peak area obtained from crystalline mebendazole.

(E) Similarly, proceeding as in parts A, B, or C above but substituting oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, or cambendazole for fenbendazole, the corresponding stabilized amorphous compositions are produced.

### EXAMPLE 3

(A) Ten grams of fenbendazole is dissolved in 50 ml of concentrated formic acid (95-97%). The resulting solution is then spray dried using a conventional spray drying apparatus to yield amorphous fenbendazole showing less than 10% of the peak area of crystalline fenbendazole by the X-ray diffraction procedure of Example 1.

(B) Similarly, proceeding as in part A above but substituting albendazole, mebendazole, triclabendazole, oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, or cambendazole for fenbendazole, the corresponding stabilized amorphous compositions are produced.

### EXAMPLE 4

(A) Ten grams of fenbendazole and 0.02 grams of Methocel A-15 are dissolved in 50 ml concentrated formic acid (95-97%). The resulting solution is spray dried using a conventional spray drying apparatus to yield amorphous fenbendazole with Methocel A-15 present showing less than 10% of the peak area of crystalline



-32-

fenbendazole by the X-ray diffraction procedure of Example 1.

(B) Similarly, proceeding as in part A above but substituting albendazole, mebendazole, triclabendazole, oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, or cambendazole for fenbendazole, the corresponding stabilized amorphous compositions are produced which show less than 10% of the peak area of the corresponding crystalline compound by the X-ray diffraction procedure of Example 1.

#### EXAMPLE 5

##### (Injectable Formulation)

(A) A formulation suitable for injection was prepared as follows:

---

amorphous fenbendazole	5.0 g
Methocel • A4C	0.3 g
methyl paraben	0.01 %
propyl paraben	0.005 %
polyethylene glycol 4000	1.0 g
sterile water for injection qs	100.0 ml

---

The formulation was prepared as follows: The polyethylene glycol was dissolved in a small amount of water at 70°C. To this was added the fenbendazole (with or without stabilizer polymer present), methyl paraben, and propyl paraben. The methyl cellulose was then dissolved in about 10 mL of water, and the resulting solution stirred into the amorphous fenbendazole solution and brought to volume with distilled water.

(B) Similarly, proceeding as in part A above but substituting albendazole, mebendazole, oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, triclabendazole or cambendazole for fenbendazole, the corresponding amorphous formulations are produced.

1804Y

25320-FF

EXAMPLE 6

## (Suspension Formulations)

(A) A formulation suitable for oral or intraruminal administration was prepared as follows:

5

---

	amorphous fenbendazole	1.5 g
	Methocel • A-15	0.25 g
	methyl paraben	0.01 %
	propyl paraben	0.005 %
	Keltrol •	1.5 g
10	polyethylene glycol 4000	2.0 g
	Carbopol	1.5 g
	water	qs
		100.0 ml

---

The formulation was prepared as in Example 5 above, with the Keltrol • added in solution with the methyl cellulose.

15

(B) Another formulation suitable for oral or intraruminal administration was prepared as follows:

---

	amorphous fenbendazole	5.0 g
	methyl cellulose	0.4 g
	methyl paraben	0.01 %
20	propyl paraben	0.005 %
	Keltrol •	1.0 g
	polyethylene glycol 4000	2.0 g
	Carbopol	1.5 g
	water	qs
		100.0 ml

---

25 The formulation was prepared as in Example 5 above, with the Keltrol • and Carbopol added in solution with the methyl cellulose.

(C) Another formulation suitable for oral or intraruminal administration was prepared as follows:

30

---

	amorphous fenbendazole	12.0 g
	methyl cellulose	1.2 g
	methyl paraben	0.01 %
	propyl paraben	0.005 %
	Keltrol •	1.0 g
	polyethylene glycol 4000	1.0 g
35	Carbopol	1.0 g
	water	qs
		100.0 ml

---

1804Y

25320-FF

The formulation was prepared as in part B above.

EXAMPLE 7

(Top Dress Formulations)

- 5 (A) A "crumble" formulation suitable for use as a top dress on animal feed was prepared as follows:

	amorphous fenbendazole	50.0 mg
	methyl cellulose	0.25 mg
	lactose	5.0 g
10	corn syrup	0.5 g

- 15 The formulation was prepared as follows: the powdered amorphous fenbendazole (with or without stabilizer polymer present), methyl cellulose, and lactose are blended together and granulated with the corn syrup. After drying, the granules are tabletted and the tablets crushed to particles less than 5 mm in diameter.

- 20 (B) Another formulation suitable for use as a top dress on animal feed was prepared as follows:

	amorphous oxfendazole	1.5 g
	amorphous triclabendazole	1.0 g
	methyl cellulose	5.0 mg
	Masonex	5.0 g
	wheat bran	0.7 g

- 25 The formulation was prepared as follows: methyl cellulose is dissolved in a minimum quantity of water and the amorphous oxfendazole (with or without stabilizer polymer present) and amorphous triclabendazole (with or without stabilizer polymer present) are added. The resulting slurry is then mixed with Masonex, and then mixed with wheat bran. The resulting mixture is then dried in a tray drying oven.

- 35 (C) A suspension formulation suitable for use as a top dress on animal feed was prepared as follows:

---

	amorphous fenbendazole	10.0 g
	methyl cellulose	0.5 g
	methyl paraben	0.01 %
	propyl paraben	0.005 %
5	Keltrol	0.1 %
	polyethylene glycol 4000	2.0 g
	Carbopol	2.0 g
	water	100.0 ml
	qs	

---

10 The formulation was prepared following the same procedure as in Example 6(A).

#### EXAMPLE 8

##### (Tablet Formulations)

15 (A) A tablet formulation suitable for administration to dogs and similar mammals was prepared as follows:

---

	amorphous fenbendazole	50.0 mg
	methyl cellulose	0.1 mg
	starch	15.0 mg
20	lactose	150.0 mg
	magnesium stearate	0.2 mg

---

25 The formulation was prepared as follows: a paste is prepared using 7.5 mg of starch, the methyl cellulose, and a minimal quantity of water. The paste is then used to granulate the amorphous fenbendazole (with or without stabilizer polymer present), lactose, and remaining starch. The resulting granulate is then dried, blended with the magnesium stearate, and then tabletted.

30 (B) A tablet formulation suitable for administration to humans and similar mammals was prepared as follows:

---

amorphous mebendazole	200.0 mg
methyl cellulose	0.4 mg
microcrystalline cellulose	300.0 mg
magnesium stearate	0.4 mg

---

5

The formulation was prepared as follows: the powders are blended together and tabletted without further processing.

(C) A tablet formulation suitable for  
10 administration to cattle and similar mammals was prepared as follows:

---

amorphous fenbendazole	2.5 g
methyl cellulose	10.0 mg
15 starch	0.3 g
lactose	50.0 mg
magnesium stearate	0.2 mg

---

15

The formulation was prepared as follows: a paste is prepared using 7.5 mg of starch, the methyl cellulose,  
20 and a minimal quantity of water. The paste is then used to granulate the amorphous fenbendazole (with or without stabilizer polymer present), lactose, and remaining starch. The resulting granulate is then dried, blended with the magnesium stearate, and then tabletted.

25

#### EXAMPLE 9

The following is an experimental procedure to demonstrate the efficacy of the invention.

(A) Fifteen (15) goats, preferably from a single  
30 source, known to be infected with nematode parasites as evidenced by positive fecal egg counts are used. The animals would be preferably of one sex. They will have been to be contaminated with goat parasite eggs and larvae, particularly Ostertagia spp. (hereinafter "Ost")  
35 and Trichostrongylus spp. (hereinafter "Tri")

Treatment Groups

1. - Control
2. - 9 mg amorphous oxfendazole/kg
3. - 15 mg oxfendazole/kg

5 Animals are then subjected to necropsy on day 6 post-treatment. Gastrointestinal tract, lungs, and liver are examined using standard parasitological techniques for nematode and trematode parasites.

10

<u>Treatment</u>	<u>Percent Efficacy</u>	
	<u>Ost</u>	<u>Tri</u>
15 mg oxfendazole/kg	77%	80%
9 mg amor. oxfendazole/kg	70%	98%

15

(B) Sheep carrying nematodes with varying degrees of resistance to oxfendazole were treated with either levamisole, oxfendazole, or amorphous oxfendazole in accordance with the above procedure.

20

<u>Treatment</u>	<u>Ost</u>	<u>Tri</u>	<u>Nem</u>	<u>Oes</u>	<u>Tr. o</u>
Levamisole 6 mg/kg	98%	49%	100%	100%	37%
Oxfendazole 5 mg/kg	0%	100%	22%	100%	38%
Oxfendazole 10 mg/kg	28%	99.7%	80%	100%	62%
Am. Oxfendazole 3 mg/kg	55%	100%	57%	100%	9.5%
25 Am. Oxfendazole 6 mg/kg	22%	100%	82%	100%	69%

Ost = Ostertagia spp.

Tri = Trichostrongylus spp.

Nem = Nematodirus spp.

30 Oes = Oesophagostomum spp.

Tr.o = Trichuris ovis

The above two studies suggest that amorphous oxfendazole is approximately equivalent in efficacy to oxfendazole, but at a reduced dose of only about 60% of

35

that required for oxfendazole. No toxicity was seen at the above dosage levels.

# EXAMPLE 10

5 The following is an experimental procedure to demonstrate blood plasma levels of the active compounds administered.

Dogs were administered orally either amorphous or crystalline oxfendazole at a dose of 10 mg/kg.

10 Blood samples were drawn and analyzed before administration and on days 1, 2, 3, 7, 10, and 13 following administration. The area under the curve was calculated for plasma concentration vs time profile. Dogs treated with amorphous oxfendazole evinced a higher plasma level of oxfendazole than dogs treated with  
15 oxfendazole in commercially available form.

		Area Under the Curve (ng/ml hr)	
		<u>Amorphous Ox.</u>	<u>Crystalline Ox.</u>
20	A	20465.0	2700.0
	B	9717.5	2622.0
	C	11592.5	2130.0
	D	24245.0	3341.0
	E	12653.8	3107.5
	F	25475.0	4149.5
25	mean (n = 6)	17358.1	3008.4
	+/- S.D.	6880.7	698.4

A similar experiment with sheep showed similar increases in the area under the plasma concentration curve for amorphous oxfendazole over crystalline  
30 oxfendazole.

35

EXAMPLE 11

The dissolution rate of amorphous fenbendazole versus crystalline fenbendazole at pH 2 was studied as a model for showing the bioavailability of the amorphous compound. Over time it was shown that amorphous fenbendazole is more soluble than crystalline fenbendazole and remains more soluble over time.

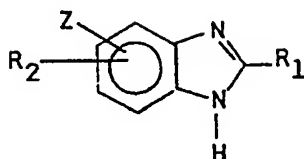
Time(min)	% Dissolved	
	crys. Fen.	amor. Fen.
5	21	73
15	22	91
30	46	125
60	41	130
90	25	112

Similarly proceeding as above, similar dissolution rates were found for triclabendazole, mebendazole, and the other benzimidazole derivatives.



CLAIMS:

1. An amorphous compound of formula 1



(1)

or a pharmaceutically acceptable salt thereof, wherein

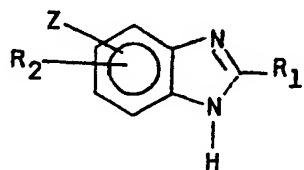
$Z$  is  $-H$  or halo;

$R_1$  is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or  $R_1$  is  $-SCH_3$ ,  $-NHCOOR_3$ ,  $-NHCSOR_3$ , or  $-NHCOSR_3$  where  $R_3$  is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

$R_2$  is H, R, or  $-XR$ , where X is O, S,  $-C(O)-$ , or  $-NHCOO-$ ; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy or alkoxy.

2. The amorphous compound of Claim 1 wherein said compound is albendazole, fenbendazole, cyclobendazole, mebendazole, flubendazole, oxibendazole, parbendazole, thiabendazole, triclabendazole, or cambendazole.

3. A stable amorphous composition comprising a stabilizing amount of a stabilizer polymer; and an amorphous compound of formula 1



(1)

or a pharmaceutically acceptable salt, wherein Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSR<sub>3</sub>, or -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-, or -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy or alkoxy.

4. The amorphous composition of Claim 3 wherein said compound is albendazole, fenbendazole, cyclobendazole, mebendazole, flubendazole, oxibendazole, parbendazole, thiabendazole, triclabendazole, or cambendazole.

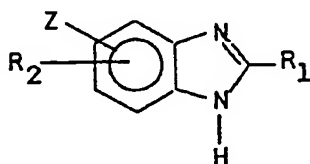
5. The amorphous composition of Claim 3 or 4 wherein said stabilizer polymer comprises cellulosic derivatives, polyvinyl pyrrolidone and derivatives, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, arabinogalactans, galactomannans, and dextrans.

6. The amorphous composition of Claim 5 wherein said stabilizer polymer is a cellulose derivative such as methylcellulose, Methocel<sup>®</sup> A-15, Methocel<sup>®</sup> A4C, or sodium carboxymethylcellulose.

5

7. An amorphous composition, comprising an amorphous compound of formula 1

10



(1)

15 or a pharmaceutically acceptable salt, wherein Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or

20 -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-, or -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or

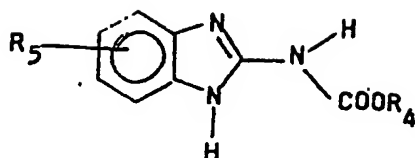
25 alkoxy;

and

a different amorphous compound of formula 1 or an amorphous compound of formula 2

30

35



(2)

5

or a pharmaceutically acceptable salt thereof,  
wherein

$R_4$  is lower alkyl; and

$R_5$  is  $-S(O)_mR_6$ ,  $-OR_6$ , or

10  $-Y_1(CH_2)_nY_2R_7$  where

$Y_1$  and  $Y_2$  are each independently O, S, or  
S(O),  $R_7$  is lower alkyl, phenyl, or naphthyl, and  
 $n$  is 1, 2, 3, or 4;

15  $R_6$  is lower alkyl, cycloalkyl, alkenyl of 3  
to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms,  
phenyl, benzyl, phenylethyl, or naphthyl; and  
 $m$  is 0 or 1.

8. The amorphous composition of Claim 7  
20 comprising an amorphous compound of formula 1 and an  
amorphous compound of formula 2.

9. The amorphous composition of Claim 8 wherein  
said compound of formula 1 is amorphous triclabendazole.  
25

10. The amorphous composition of Claim 9 wherein  
said compound of formula 2 is amorphous oxfendazole.

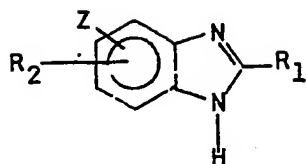
30 11. A stable amorphous composition comprising  
a stabilizing amount of a stabilizer polymer;  
an amorphous compound of formula 1

35

1804Y

25320-FF

-44-



(1)

5

or a pharmaceutically acceptable salt, wherein

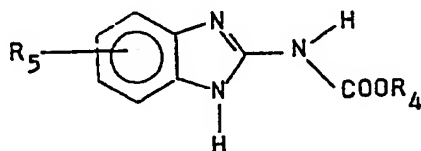
Z is -H or halo;

10  $R_1$  is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or  $R_1$  is  $-SCH_3$ ,  $-NHCOOR_3$ ,  $-NHCSOR_3$ , or  $-NHCOSR_3$  where  $R_3$  is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

15  $R_2$  is H, R, or  $-XR$ , where X is O, S,  $-C(O)-$ , or  $-NHC(O)-$ ; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or alkoxy;

and

20 a different amorphous compound of formula 1 or an amorphous compound of formula 2



(2)

25

or a pharmaceutically acceptable salt thereof,  
wherein

$R_4$  is lower alkyl; and

30  $R_5$  is  $-S(O)_m R_6$ ,  $-OR_6$ , or

$-Y_1(CH_2)_n Y_2 R_7$  where

$Y_1$  and  $Y_2$  are each independently O, S, or S(O),  $R_7$  is lower alkyl, phenyl, or naphthyl, and n is 1, 2, 3, or 4;

35

$R_6$  is lower alkyl, cycloalkyl, alkenyl of 3 to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms, phenyl, benzyl, phenylethyl, or naphthyl; and  $m$  is 0 or 1.

5

12. The amorphous composition of Claim 11 wherein said compound of formula I is amorphous tricloabendazole.

13. The amorphous composition of Claim 12 wherein 10 said compound of formula 2 is amorphous oxfendazole.

14. The amorphous composition of any one of Claims 11 to 13 wherein said stabilizer polymer comprises cellulosic derivatives, polyvinyl pyrrolidone and derivatives, 15 xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, arabino-galactans, galactomannans, and dextrans.

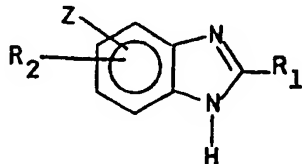
20 15. The amorphous composition of Claim 14 wherein said stabilizer polymer is a cellulosic derivative such as methylcellulose, Methocel® A-15, Methocel® A4C, or sodium carboxymethylcellulose.

25 16. A pharmaceutical or veterinary composition for the treatment of helminthiasis and/or fascioliasis, which composition comprises:

a stabilizing amount of a stabilizer polymer;  
a carrier acceptable for pharmaceutical or veterinary 30 use; and

an amorphous compound of formula 1, a combination of amorphous compounds of formula 1,

35



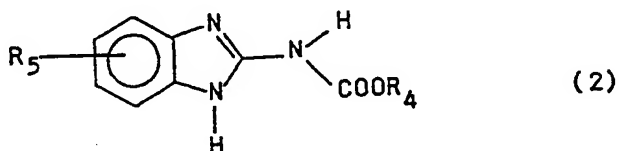
(1)

or a pharmaceutically acceptable salt, wherein  
Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring  
containing 1, 2, or 3 heteroatoms selected from O, N, and  
S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or  
-NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl,  
alkynyl, phenyl, or naphthyl; and

R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-, or  
-NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl,  
optionally substituted with halo, alkyl, hydroxy, or  
alkoxy;

or a combination of an amorphous compound of formula 1  
and an amorphous compound of formula 2



or a pharmaceutically acceptable salt thereof,  
wherein

R<sub>4</sub> is lower alkyl; and

R<sub>5</sub> is -S(O)<sub>m</sub>R<sub>6</sub>, -OR<sub>6</sub>, or

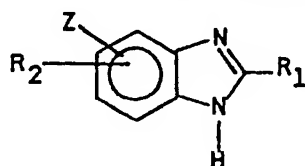
-Y<sub>1</sub>(CH<sub>2</sub>)<sub>n</sub>Y<sub>2</sub>R<sub>7</sub> where

Y<sub>1</sub> and Y<sub>2</sub> are each independently O, S, or S(O),  
R<sub>7</sub> is lower alkyl, phenyl, or naphthyl, and n is 1, 2,  
3, or 4;

R<sub>6</sub> is lower alkyl, cycloalkyl, alkenyl of 3 to 7  
carbon atoms, alkynyl of 3 to 7 carbon atoms, phenyl,  
benzyl, phenylethyl, or naphthyl; and

m is 0 or 1.

17. The composition of Claim 16 which comprises:  
 0.001%-50% stabilizer polymer;  
 1%-99% carrier acceptable for pharmaceutical or  
 veterinary use;  
 1%-95% amorphous compound of formula 1

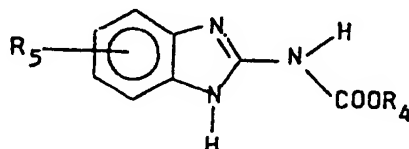


(1)

- or a pharmaceutically acceptable salt thereof, wherein  
 Z is -H or halo;

- R<sub>1</sub> is a five-membered heteroaromatic ring  
 containing 1, 2, or 3 heteroatoms selected from O,  
 N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>,  
 -NHCSOR<sub>3</sub>, or -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl,  
 cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl;  
 and

- R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-,  
 or -NHCOO-; and R is alkyl, cycloalkyl, aryl or  
 aryl-alkyl, optionally substituted with halo, alkyl,  
 hydroxy, or alkoxy; and  
 0%-95% amorphous compound of formula 2



(2)

- or a pharmaceutically acceptable salt thereof,  
 wherein  
 R<sub>4</sub> is lower alkyl; and

- R<sub>5</sub> is -S(O)<sub>m</sub>R<sub>6</sub>, -OR<sub>6</sub>, or -Y<sub>1</sub>(CH<sub>2</sub>)<sub>n</sub>Y<sub>2</sub>R<sub>7</sub> where  
 Y<sub>1</sub> and Y<sub>2</sub> are each independently O, S, or  
 S(O), R<sub>7</sub> is lower alkyl, phenyl, or naphthyl, and  
 n is 1, 2, 3, or 4;

- R<sub>6</sub> is lower alkyl, cycloalkyl, alkenyl of 3  
 to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms,  
 phenyl, benzyl, phenylethyl, or naphthyl; and  
 m is 0 or 1.



18. The composition of Claim 16 or 17 wherein said amorphous compound of formula 1 is albendazole, mebendazole, oxibendazole, parbendazole, flubendazole, cyclobendazole, thiabendazole, triclabendazole, cambendazole or fenben-  
5 dazole.

19. The composition of Claim 18 wherein said compound of formula 1 is triclabendazole, and said compound of formula 2 is oxfendazole.

0 20. The amorphous composition of any one of Claims 16 to 19 wherein said stabilizer polymer comprises cellulosic derivatives, polyvinyl pyrrolidone and derivatives, xanthan gums, pectins, alginates, tragacanth and derivatives,  
5 gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, arabino-galactans, galactomannans, and dextrans.

21. The amorphous composition of Claim 20 wherein  
10 said stabilizer polymer is a cellulosic derivative such as methylcellulose, Methocel<sup>®</sup> A-15, Methocel<sup>®</sup> A4C, or sodium carboxymethylcellulose.

22. The composition of any one of Claims 16 to  
25 21 wherein said amorphous compound of formula 1 and said stabilizer polymer are present in a ratio between about 1000:1 and about 1:90, preferably between about 100:1 and about 5:1.

30 23. The composition of Claim 22 which is suitable for oral administration, or for parenteral or intraruminal injection, wherein

said amorphous compound of formula 1 is present in an amount between about 1% and about 40% by weight;

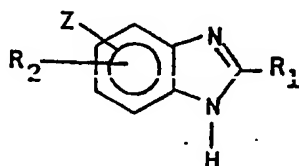
35 said stabilizer polymer is present in an amount between about 0.02% and about 3% by weight; and

said carrier acceptable for pharmaceutical or veterinary use is a liquid present in an amount between about 99% and about 57% by weight.

5           24. The composition of Claim 22 which is suitable for oral administration as a tablet or capsule, wherein  
               said amorphous compound of formula 1 is present in  
               an amount between about 15% and about 98% by weight;  
               said stabilizer polymer is present in an amount  
 10           between about 0.01% and about 85% by weight; and  
               said carrier acceptable for pharmaceutical or  
               veterinary use is a solid present in an amount between  
               about 85% and about 1% by weight.

15           25. The use of an amorphous compound of formula 1 to prepare a pharmaceutical or veterinary composition for the treatment of helminthiasis and/or fascioliasis

20

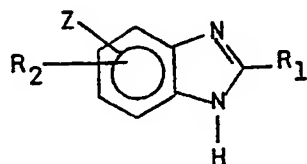


(1)

25   or a pharmaceutically acceptable salt, wherein  
           Z is -H or halo;  
           R<sub>1</sub> is a five-membered heteroaromatic ring  
           containing 1, 2, or 3 heteroatoms selected from O, N, and  
           S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or  
 30    -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl,  
           alkynyl, phenyl, or naphthyl; and  
           R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-, or  
           -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl,  
           optionally substituted with halo, alkyl, hydroxy, or  
 35    alkoxy.

26. The use of a stabilizer polymer with an amorphous compound of formula 1, a combination of amorphous compounds of formula 1

5



(1)

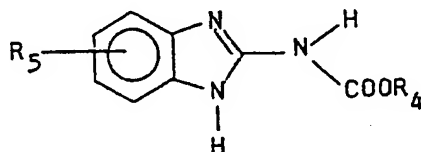
10 or a pharmaceutically acceptable salt, wherein Z is -H or halo;

R<sub>1</sub> is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or R<sub>1</sub> is -SCH<sub>3</sub>, -NHCOOR<sub>3</sub>, -NHCSOR<sub>3</sub>, or  
15 -NHCOSR<sub>3</sub> where R<sub>3</sub> is alkyl, cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and

R<sub>2</sub> is H, R, or -XR, where X is O, S, -C(O)-, or -NHCOO-; and R is alkyl, cycloalkyl, aryl or aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or  
20 alkoxy,

or a combination of an amorphous compound of formula 1 and an amorphous compound of formula 2

25



(2)

or a pharmaceutically acceptable salt thereof, wherein

30 R<sub>4</sub> is lower alkyl; and

R<sub>5</sub> is -S(O)<sub>m</sub>R<sub>6</sub>, -OR<sub>6</sub>, or -Y<sub>1</sub>(CH<sub>2</sub>)<sub>n</sub>Y<sub>2</sub>R<sub>7</sub> where

Y<sub>1</sub> and Y<sub>2</sub> are each independently O, S, or S(O), R<sub>7</sub> is lower alkyl, phenyl, or naphthyl, and  
35 n is 1, 2, 3, or 4;

$R_6$  is lower alkyl, cycloalkyl, alkenyl of 3 to 7 carbon atoms, alkynyl of 3 to 7 carbon atoms, phenyl, benzyl, phenylethyl, or naphthyl; and  $m$  is 0 or 1;

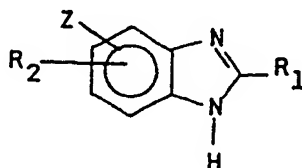
5 to prepare a veterinary composition for the treatment of helminthiasis and/or fascioliasis.

27. The use of Claim 26 wherein said stabilizer polymer comprises cellulosic derivatives, polyvinyl  
10 pyrrolidone and derivatives, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, arabinogalactans, galactomannans, and dextrans.

15 28. The use of Claim 27 wherein said stabilizer polymer is a cellulosic derivative such as methylcellulose, Methocel® A-15, Methocel® A4C, or sodium carboxymethylcellulose.

20 29. A process for preparing an amorphous anthelmintic compound of formula 1

25



(1)

30 or a pharmaceutically acceptable salt, wherein Z is -H or halo;  $R_1$  is a five-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms selected from O, N, and S, or  $R_1$  is  $-SCH_3$ ,  $-NHCOOR_3$ ,  $-NHCSOR_3$ , or  $-NHCOSR_3$  where  $R_3$  is alkyl,  
35 cycloalkyl, alkenyl, alkynyl, phenyl, or naphthyl; and  $R_2$  is H, R, or  $-XR$ ; where X is O, S,  $-C(O)-$ ; or  $-NHCOO-$ ; and R is alkyl, cycloalkyl, aryl or

aryl-alkyl, optionally substituted with halo, alkyl, hydroxy, or alkoxy, which process comprises:

5 A. (a) dissolving a compound of formula 1 in a base or acid to dissolve or solubilize said compound of formula 1, followed by

(b) adding an amount of an acid or base under conditions to precipitate said compound of formula 1 in an amorphous form; or

10 B. (a) dissolving a compound of formula 1 in an acid or base to dissolve or solubilize said compound of formula 1, followed by

(b) spray drying the solution of step (a) to produce an amorphous compound of formula 1; or

15 C. (a) dissolving a compound of formula 1 in an acid or base solution containing a stabilizing amount of a stabilizer polymer, followed by

(b) spray drying the solution of step (a) to produce an amorphous compound of formula 1; or

20 D. (a) dissolving a compound of formula 1 in an acid or base within a first pH range to dissolve or solubilize said compound of formula 1, followed by

(b) adding a stabilizing amount of a stabilizer polymer in a solution of a second pH range opposite to that used in step (a), followed by

25 (c) adding acid or base to reestablish a third acid or base pH range on the same side of the pH scale as said first pH range to form an amorphous form of a compound of formula 1.

30 30. The process of Claim 29 wherein said acid comprises concentrated acetic acid, propionic acid, hydrochloric acid, phosphoric acid, formic acid, and nitric acid.

35 31. The process of Claim 29 or 30 wherein the pH range of step A(a), B(a), C(a), or D(a) is lower than about 3.

32. The process of Claim 29 or 30 wherein the pH range of step A(a), B(a), C(a), or D(a) is between about 8 and 10.

5 33. The process of Claim 29 or 30 wherein the pH range of step A(b), or D(c) is between about 4 and 6.

10 34. The process of any one of Claims 29 to 33 wherein said base comprises ammonium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, sodium methylate, sodium ethylate, sodium hydride, triethylamine and pyridine.

15 35. The process of any one of Claims 29 to 34 wherein said stabilizer polymer comprises cellulosic derivatives, polyvinyl pyrrolidone and derivatives, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbial sources, 20 arabinogalactans, galactomannans, and dextrans.

25 36. The process of Claim 35 wherein said stabilizer polymer is a cellulosic derivative such as methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, and hydroxypropylcellulose.

30

35



European Patent  
Office

# EUROPEAN SEARCH REPORT

224249

Application number

## DOCUMENTS CONSIDERED TO BE RELEVANT

EP 86116396.2

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	DE - A1 - 3 347 579 (HOECHST AG) * Claims; pages 4,5 * --	1,2,7, 16,25, 29	C 07 D 235/30 C 07 D 235/28 C 07 D 235/18 C 07 D 417/04 A 61 K 31/415 A 61 K 31/425
A	CHEMICAL ABSTRACTS, vol. 93, no. 6, August 11, 1980, Columbus, Ohio, USA FREY, M.H.; KELLER, H. "Bioavail- ability of benzimidazole anthel- mintics from different pharma- ceutical preparations in the horse" page 456, column 1, abstract-no. 53 873p & Prakt. Tierarzt 1980, 61(3), 234, 239-40 --	1,2,7, 16,25, 29	
A	EP - A1 - 0 131 762 (SUMITOMO CORP.) * Claims * -----	1,2,7, 16,25, 29	TECHNICAL FIELDS SEARCHED (Int. Cl. 4)  C 07 D 235/00 C 07 D 417/00
The present search report has been drawn up for all claims			
Place of search VIENNA	Date of completion of the search 02-03-1987	Examiner BRUS	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

**THIS PAGE BLANK (USPTO)**



**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

**THIS PAGE BLANK (USPTO)**